PROGRESS REPORT FOR AINGRA07016

PROJECT TITLE | Using phase transitions to trigger drug release from nanostructured liquid crystalline drug delivery systems

INVESTIGATOR(S) | Institution and Department
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Specialist Committee | N

SCIENTIFIC OBJECTIVES

The primary objective of these studies was to determine the susceptibility of nanostructured amphiphile-based liquid crystalline matrices to phase changes under the influence of external stimuli. In particular the ability to induce phase changes between liquid crystalline states with varying geometric structure, such as lamellar, cubic, sponge, hexagonal and micellar systems, using stimuli including pH, temperature, light and osmotic pressure will be quantified using small angle x-ray scattering. The changes in nanostructure will be correlated with changes in drug release rates to provide proof of concept of the utility of these materials as tunable drug delivery systems.

PROGRESS REPORT and RESEARCH OUTCOMES

This grant is only half completed (5 days SAXS beamtime utilized) due to equipment malfunction that will not be remedied until 2008. The project comprises a major part of an Honours project for Ms. Fong, which will be due in October 2007, hence completion of this report now – if the further five days becomes available in 2008 the intention is that the experiments would still be completed by another researcher from this group. Approximately half of the experimental program was completed in the 5 days.

We have data that illustrates dramatic changes in drug release for changes in liquid crystalline nanostructure. Using SAXS we have investigated how additives impact on the nature of the phase present for a particular composition, pH or temperature, with a view to designing materials with ‘triggerable’ drug release.

The SAXS data obtained under the grant thus far have allowed us to design liquid crystalline systems in which we can manipulate temperature within a small range to induce a desired phase change in the liquid crystalline material, at temperatures close to physiological temperature. We have confirmed that drug release rates do in fact change at the temperatures predicted from the SAXS data. This allows us to prepare samples with the appropriate composition to conduct in vivo proof of principle studies which are currently underway, in which the material is injected subcutaneously and the phase structure, and hence drug release rate, controlled by temporary application of eg. a heat or cool pack to the surface of the skin.

The second phase of our studies was to investigate whether we could use pH in a similar manner to induce the nanostructural changes by incorporation of ionizable compounds into the phase structure. We have obtained SAXS data which shows that this is possible in principle and will complete more studies if future SAXS time becomes available.
1. Temperature induce phase changes

GMO + oleic acid mixtures

![Phase diagram](image1)

**Figure 1** - Phase diagram determined for increasing oleic acid in Myverol (GMO) under excess water conditions by indexing peak positions from SAXS I vs q plots obtained at the individual temperature/composition data points. Systems were prepared at 50% water (w/w) relative to total lipid to avoid excessive dilution and liberation of oleic acid from the matrix.

![Lattice parameter](image2)

**Figure 2** – Temperature dependence of lattice parameter for reverse cubic ($Q_{Pn3m}$) and reverse hexagonal ($H_{II}$) phases formed for Myverol (GMO) with increasing proportion of oleic acid in excess water. Over the range investigated, for a given phase structure (i.e. Q or $H_{II}$), the lattice parameter was only dependent on temperature and not on the composition, although the temperature of the phase change itself did change with temperature (see Figure 1).

Figure 1 demonstrates the change in $Q_{Pn3m} \rightarrow Q_{Pn3m} + H_{II}$ phase transition temperature with increasing oleic acid. The physiological ‘switch’ temperature of 37°C requires 2.7% oleic acid – cooling the administration site with eg. a cool pack would induce the change to $Q_{Pn3m}$ alone which has a faster drug release rate that the mixed phase system.
The lattice dimension is important in selecting the drug release rate, and knowing the dependence of lattice dimension on temperature is therefore a critical aspect of designing appropriate systems for in vivo application. The data in Figure 2 show only a slight dependence on temperature, hence indicating that a phase change is required for more dramatic changes in drug release rates. Although the different oleic acid concentrations dramatically affected the transition temperatures in Figure 1, it did not substantially alter the lattice parameter.

**Phytantriol + vitamin E acetate mixtures**

Figure 3 - Phase diagram for increasing vitamin E in phytantriol under excess water conditions, determined by indexing peak positions from SAXS I vs q plots obtained at the individual temperature, composition data points. Systems were prepared at 50% water (w/w) relative to total lipid to avoid excessive dilution and liberation of oleic acid from the matrix.

Figure 4 – Temperature dependence of lattice parameter for reverse cubic (Pn3m) and reverse hexagonal (HII) phases formed for phytantriol with increasing proportion of vitamin E in excess water. Over the range investigated, for a given phase structure (i.e. Q or HII), the lattice parameter was only dependent on temperature and not on the composition, although the temperature of the phase change itself did change with temperature (see Figure 3).

Figure 3 demonstrates the change in Q_{Pn3m} \rightarrow Q_{Pn3m} + H_{II} \rightarrow H_{II} phase transition temperatures with increasing vitamin E acetate content in phytantriol. In this case one could envisage the application of a heat pack after administration of the 2.5% composition would induce a change to the HII phase, and consequent change in drug release rate. Because the phytantriol based systems undergo the full change between cubic and hexagonal phase over a reasonable temperature range around physiological temperature, it is likely to be the most useful one in the proof of concept in vivo studies. This data is consistent with data obtained by Dong et al. under AINGRA05185 (Dong et al. Langmuir 22 (2006) 9512-9518), but in significantly greater detail, allowing the accurate selection of the optimal composition to take into in vivo studies.

Again the data in Figure 4 confirm the small dependence of lattice dimension on temperature, but also indicates that, with a smaller lattice overall, phytantriol will give slower drug release overall compared to the GMO system. Again, although the vitamin E acetate provided significant changes in transition temperature in Figure 3, the lattice parameter was not substantially affected by the presence of up to 3.5% vitamin E acetate within a particular phase structure.
2. pH induced phase changes

This data shows that with increasing pH there is a slight expansion of the overall lattice dimension for these systems. For the GMO based system the $H_{II}$ phase coexisted with the $Q_{III}$ phase up to neutral pH, while for the phytantriol system there was a clear switch over from $H_{II}$ to $Q_{II}$ at pH 4. This indicates that the phytantriol system is likely to be particularly useful as a pH triggered release system, but more work needs to be completed with this system to determine its applicability across a more focused range of pH values, and with varying oleic acid content. Acids with different pKas will also be investigated.

**Figure 5** – Dependence of phase structure and lattice dimension on pH for GMO+3% oleic acid, and Phytantriol+3.55% oleic acid lipid mixtures in excess aqueous solution.

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**PhD STUDENTS**
